

MESOTHELIN BINDING PROTEINS

CROSS-REFERENCE

[0001] This application claims the benefit of U.S. Provisional Application Nos. 62/505,719 filed on May 12, 2017 and 62/657,417 filed April 13, 2018, each incorporated by reference herein in its entirety.

SEQUENCE LISTING

[0002] The instant application contains a Sequence Listing which has been submitted electronically in ASCII format and is hereby incorporated by reference in its entirety. Said ASCII copy, created on May 11, 2018, is named 47517-719_601_SL.txt and is 145,039 bytes in size.

INCORPORATION BY REFERENCE

[0003] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference, and as if set forth in their entireties.

BACKGROUND OF THE INVENTION

[0004] The present disclosure provides mesothelin (MSLN) binding proteins which can be used for diagnosing and treating indications correlated to the expression of MSLN. Mesothelin (MSLN) is a GPI-linked membrane bound tumor antigen MSLN is overexpressed ovarian, pancreatic, lung and triple-negative breast cancers and mesothelioma. Normal tissue expression of MSLN is restricted to single-cell, mesothelial layers lining the pleural, pericardial, and peritoneal cavities. Overexpression of MSLN is associated with poor prognosis in lung adenocarcinoma and triple-negative breast cancer. MSLN has been used as cancer antigen for numerous modalities, including immunotoxins, vaccines, antibody drug conjugates and CAR-T cells. Early signs of clinical efficacy have validated MSLN as a target, but therapies with improved efficacy are needed to treat MSLN-expressing cancers.

SUMMARY OF THE INVENTION

[0004a] In one aspect, provided herein is a single domain mesothelin binding protein, wherein the single domain mesothelin protein comprises a sequence of SEQ ID NO: 31.

[0004b] In one aspect, provided herein is a single domain mesothelin binding protein, wherein the single domain mesothelin protein comprises a sequence selected from the group consisting of SEQ ID NOs: 1-16, 18-25 and 28-29.

[0004c] In one aspect, provided herein is a single domain mesothelin binding protein, wherein the single domain mesothelin protein comprises the following formula:

f1-r1-f2-r2-f3-r3-f4

wherein, r1 is CDR1; r2 is CDR2; and r3 CDR3; and

wherein f1, f2, f3 and f4 are framework residues, and

wherein:

- (i) the CDR1 comprises the sequence GSTSSINTMY (SEQ ID NO: 82), the CDR2 comprises the sequence FISSGGSTNVRDSVKGRFS (SEQ ID NO: 121), and the CDR3 comprises the sequence YIPLRGTLHDY (SEQ ID NO: 160);
- (ii) the CDR1 comprises the sequence GSTSSINTMY (SEQ ID NO: 82), the CDR2 comprises TINRGGSTNVRDSVKGRFS (SEQ ID NO: 125), and the CDR3 comprises the sequence YIPYGGTLHDF (SEQ ID NO: 164);
- (iii) the CDR1 comprises the sequence TTFSINSMS (SEQ ID NO: 87), the CDR2 comprises the sequence VITNRGTTSYADSVKGRFT (SEQ ID NO: 126), the CDR3 comprises the sequence IADWRGY (SEQ ID NO: 153);
- (iv) the CDR1 comprises the sequence AIGSINSMS (SEQ ID NO: 85), the CDR2 comprises the sequence VITDRGSTSYADSVKGRFT (SEQ ID NO: 114), the CDR3 comprises the sequence IADWRGY (SEQ ID NO: 153);
- (v) the CDR1 comprises the sequence GLTFGVYGME (SEQ ID NO: 74), the CDR2 comprises the sequence SHTSTGYVYYRDSVKGRFT (SEQ ID NO: 113), and the CDR3 comprises the sequence NRGSYEY (SEQ ID NO: 152);
- (vi) the CDR1 comprises the sequence GSTSNINMR (SEQ ID NO: 66), the CDR2 comprises the sequence VITRGGYAIYLDVAVKGRFT (SEQ ID NO: 105), and the CDR3 comprises the sequence DRVEGTSGGPQLRDY (SEQ ID NO: 144); or
- (vii) the CDR1 comprises the sequence GTTYTFDLMS (SEQ ID NO: 65), the CDR2 comprises the sequence SISSDGRTSYADSVRGRFT (SEQ ID NO: 104), and the CDR3 comprises the sequence QRSGVRAF (SEQ ID NO: 143).

[0004d] In one aspect, provided herein is a polynucleotide encoding the single domain mesothelin binding protein as described herein.

[0004e] In one aspect, provided herein is a polynucleotide encoding a single domain mesothelin binding protein, wherein the single domain mesothelin binding protein comprises the following formula:

f1-r1-f2-r2-f3-r3-f4

wherein, r1 is CDR1; r2 is CDR2; and r3 CDR3; and wherein f1, f2, f3 and f4 are framework residues, and wherein:

- (i) the CDR1 comprises the sequence GSTFSIRAMR (SEQ ID NO: 88), the CDR2 comprises the sequence VIYGSSTYYADAVKGRFT (SEQ ID NO: 127), and the CDR3 comprises the sequence DTIGTARDY (SEQ ID NO: 166);

- (ii) the CDR1 comprises the sequence GRTSTIDTMY (SEQ ID NO: 89), the CDR2 comprises YVTSRGTSNVADSVKGRFT (SEQ ID NO: 128), and the CDR3 comprises the sequence RTTSYPVDF (SEQ ID NO: 167);
- (iii) the CDR1 comprises the sequence GSTSSINTMY (SEQ ID NO: 82), the CDR2 comprises the sequence FISSGGSTNVRDSVKGRFT (SEQ ID NO: 132), the CDR3 comprises the sequence YIPYGGTLHDF (SEQ ID NO: 164);
- (iv) the CDR1 comprises the sequence GGDWSANFMY (SEQ ID NO: 54), the CDR2 comprises the sequence RISGRGVVDYVESVKGRFT (SEQ ID NO: 130), the CDR3 comprises the sequence ASY (SEQ ID NO: 169); or
- (v) the CDR1 comprises the sequence GSTFRIRVMR (SEQ ID NO: 79), the CDR2 comprises the sequence VISGSSTYYADSVKGRFT (SEQ ID NO: 118), and the CDR3 comprises the sequence DDSGIARDY (SEQ ID NO: 157).

[0004f] In one aspect, provided herein is a use of the single domain mesothelin binding protein as described herein in the manufacture of a medicament for the treatment or amelioration of a proliferative disease, or a tumorous disease.

[0004g] In one aspect, provided herein is a use of the polynucleotide as described herein in the manufacture of a medicament for use the treatment or amelioration of a proliferative disease, or a tumorous disease.

[0005] One embodiment provides a single domain mesothelin binding protein, wherein said protein comprises one or more conserved regions comprising a sequence identical to or comprising one or more amino acid residue substitutions relative to SEQ ID NO: 41, 42, 43, or 44. In some embodiments, said protein comprises a conserved region comprising a sequence identical to or comprising one or more amino acid residue substitutions relative to SEQ ID NO: